REMARKS

Claims 1, 3-7 and 9-17 are pending in the application. Claims 1, 3-7 and 9-17 are rejected. Claims 1, 3, 7, 9, 12, 13, and 17 are amended herein without prejudice and without acquiescence. Support for claim amendments can be found throughout the specification, for example paragraphs [0041], [0055], [0069]-[0073]. Claims 6 and 17 have been canceled without prejudice and without acquiescence. Applicants reserve the right to pursue amended and or canceled material in a continuation and/or divisional application.

The issues outstanding in this application are as follows:

- Claims 1, 3-7, and 9-17 have been rejected under 35 U.S.C. § 112 1¶, in which the Office Action alleges that the claimed subject matter is not enabled.

- Claims 1, 3-7, and 9-17 have been rejected under 35 U.S.C. § 112 1¶, in which the Office Action alleges that the claimed subject matter is not described.

- Claims 1, 3-7, and 9-17 have been rejected under 35 U.S.C. § 102(e), in which the Office Action alleges that the claimed subject matter is anticipated by US Patent 6,420,526 or 6,504,010.

Applicants respectfully traverses the outstanding rejections, and Applicants respectfully request reconsideration and withdrawal thereof in light of the amendments and remarks contained herein

I. Issues under 35 U.S.C. § 112, first paragraph

A. Claims 1, 3-7 and 9-17 stand rejected under 3 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons set forth in the previous Office Action, mailed 2/27/04. Applicants traverse.

Independent claims 1, 7, and 12, and their dependents concern methods of modulating an inflammatory and immune response, and decreasing myeloid cell activation by decreasing or altering the activity of the DAP12/TREM-1 complex.

The examiner asserts that the specification does not adequately teach how to effectively modulate an immune response or decrease myeloid cell activation or modulate an inflammatory response by administering an effective amount of *any* compound to decrease myeloid cell activation, or *any* compound that is a competitive inhibitor of the ligand to TREM-1 or a polypeptide comprising the amino acid sequence of SEQ.ID.NO:2 or a functional equivalent thereof (emphasis added). Applicants traverse.

In order to advance prosecution of the patent application claims 1 and 7 have been amended without prejudice and without acquiescence clarifying the scope of the invention to read on a soluble variant of TREM-1 in which the variant lacks a functional transmembrane region. With the level of skill in the art, the Applicants assert that one would be able to make and use soluble variants thereof. Although the specification does not teach how to make every soluble variant of TREM-1 in the claimed invention, paragraphs [0035], [0055], and [0069]-[0073] disclose functional equivalent and soluble variants of the TREM-1 splice variant that would be attained by conventional and routinely practiced molecular biology techniques used by those in the art.

Yet further, Applicants have amended claims 1, 12, 13 and 14 without prejudice and without acquiescence to clarify the scope of the invention such that the claims read to "decrease" the activity of the DAP12/TREM-1 complex.

1. Now, turning to various specific issues raised by the Examinar, Applicants assert that the Declaration under 37 C.F.R. § 1.132 by Gingras dated May 27, 2004 in view of

Bouchon *et al.* (2001, Nature, 410, 1103-1107) provides conformation that the disclosure by the Applicant's is enabled. The Examiner states that Bouchon *et al.* "teach a very specific mTREM-1/IgG_1 fusion protein" is incorrect since Bouchon *et al.* also teach that mTREM-1/IgG_1 is effective when the IgG_1-F_c portion of the fusion protein was mutated to inhibit F_c receptor binding. Therefore, the observed modulated immune response is a function of soluble TREM-1 and not IgG_1, clearly congruent to the Applicants' claimed invention.

2. The Examiner asserts that "no animal studies were used to study the effectively to modulate an immune response by administering an effective amount of *any* compound to decrease myeloid cell activation, or *any* compound that is a competitive inhibitor of the ligand to TREM-1 or a polypeptide comprising the amino acid sequence of SEQ.ID.NO:2 or a functional equivalent thereof" (emphasis added). Further, the Examiner states that the specification "...only states that it is envisioned that administering of TREM-1 splice variant may resulting down regulation of the inflammatory response." Clearly stated, the Declaration under 37 C.F.R. § 1.132 by Dr. Gingras on May 27, 2004 discloses that the teachings of the present invention show that a soluble TREM-1 inhibits cell functions, i.e. inflammatory response, that are activated by TREM-1 in a mouse model. Therefore, the Examiner cannot conclude the lack of reported/documented *in vivo* use of the invention. In addition, the Examiner cannot conclude the inability to extrapolate *in vitro* data into an effective *in vivo* therapeutic treatment.

3. With respect to the reasonable doubt that the skilled artisan could predict the efficacy of the claimed method, the Examiner refers the Applicants to Cochlavius *et al.* (Modern Drug Discovery, 2003, 33-38) and claims that it teaches that "...defense mechanisms are still poorly understood, they provide some hints as to why many potential therapeutics perform marvelously *in vitro* but a fairly high portion of them still fail *in vivo*." This is not an uncommon statement in pharmaceutical drug research and development. However, the article supports the claimed invention by stating "promising strategies that have already been investigated include...the disruption of signaling pathways...." The article states that a chimeric antibody that neutralizes TNF-α, Remicade, inhibits inflammation and reduces swelling in rheumatoid arthritis and has generated revenue of $1.2 billion in 2002. The Examiner's reference to Feldman *et al.* (Transplant. Proc. 1998, 30, 4126-4127), "there are a number of pathways that become engaged and effective therapy in immune

inflammatory diseases such as rheumatoid arthritis, will come from therapy aimed at several points in the disease pathway", is incorrect since Remicade is a monoclonal antibody against TNF-α that is effective in treating rheumatoid arthritis. Furthermore, Zenapax and Simulect, block the IL-2 signaling pathway, and both have been proven to be efficient in preventing kidney transplant rejection. The Examiner's reference to Van Noort *et al.* (International Review of Cytology, 1998, v. 178, ppg 127-204) and the effect of genetic, environment and hormonal composition can effect the immune response in a host is an argument lacks significance and is therefore refuted. It is obvious that side effects or inactivity of any pharmaceutical compound will be reflected in the genetic, environmental, and hormonal composition of the recipient. As with all research endeavors, an amount of uncertainty exists, but to conclude that this invention is "fraught with uncertainties" is an overstatement. In light of the Specification, the Declaration filed by Dr. Gingras on May 27, 2004, and the scientific research articles cited above, there is clearly a reasonable amount of predicted efficacy of the pending claims.

4. Due to the absence of *in vivo* clinical data the Examiner states that the claims are unpredictable for a variety of reasons as mentioned on page 1338, footnote 7 of *Ex parte* Aggarwal, 23 USPQ 2d 1334 (PTO Bd. Pat. App. & Inter. 1992). The Examiner argues that (1), the polypeptide may be inactivated before producing an effect; (2), the polypeptide may not reach the target area or may be absorbed by fluids, cell, and tissues where the polypeptide has no effect; and (3) unknown properties, which may make the protein unsuitable for *in vivo* therapeutic use. However, 76% of mice injected intraperitoneally with produced soluble TREM-1 survived endotoxic shock (Bouchon *et al.* (2001) Nature, 410, 1103-1107), indicating that the claimed invention could in fact elicit a biological response, contrary to the Examiners abovementioned statements.

5. In regard to the unpredictability of protein chemistry and which changes can be tolerated in a polypeptide's amino acid sequence to maintain similar functionality, the Applicants assert that using the state of the art and the Applicants' written disclosures, a person of ordinary skill in the art could produce and screen soluble variants of TREM-1 without undue experimentation. See *In re Wands* 8 USPQ2d 1400, 1404.

Thus, the disclosure of these operative embodiments enables one of skill in the art to make and/or use the claimed invention without undue experimentation, and the Applicants

respectfully request removal of this rejection in view of the above amendments and arguments.

II. Issues under 35 U.S.C. § 112, first paragraph

A. Claims 1, 3-7 and 9-17 stand rejected under 3 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action, mailed 2/27/04. Applicants traverse.

Independent claims 1, 7, and 12, and their dependents concern methods of modulating an inflammatory and immune response, and decreasing myeloid cell activation by decreasing or altering the activity of the DAP12/TREM-1 complex.

1. The Examiner states that a description of a protein by functional language in the absence of a structure is not considered sufficient to show possession of the claimed invention and cites *Fiers v. Sagano* 25 U.S.P.Q. 1605-1606 and *In re Wilder* 222 U.S.P.Q. 372-373. According to the Federal Register vol. 66, No. 4/Friday, January 5, 2001, the written description requirement for claims drawn to a genus may be satisfied through structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics. In order to advance prosecution of the patent application the Applicants have amended claims 1 and 7 without prejudice and without acquiescence to read a soluble polypeptide variant of TREM-1 that lacks a functional transmembrane region. A specification may, within the meaning of 35 U.S.C. § 112 paragraph 1, contain a written description of a broadly claimed invention without describing all species that the claim encompasses (See *Utter v. Hiraga*, 845 F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed. Cir. 1998). The disclosure of the sequences of TREM-1 and the identity of the transmembrane region of TREM-1, as well as the disclosure of SEQ.ID.NO:2 (TREM-1 lacking a transmembrane region) teaches chemical properties, i.e., amino acid sequence and chemical structure. The Declaration by Dr. Gingras filed on May 27, 2004, in view of Bouchon *et al.* (2001) Nature, 410, 1103-1107, teaches functional characteristics. Thus, the combination of

the chemical properties and functional characteristics described above, in addition to the skill and knowledge in the art for creating homologous and soluble variants of TREM-1, for example SEQ.ID.NO. 2, is sufficient to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention.

Thus, disclosure of these combined distinguishing characteristics lead one of skill in the art to the conclusion that the Applicants are in possession of the claimed invention, and the Applicants respectfully request removal of this rejection.

III. Issues under U.S.C. § 102(e)

A. Claims 1, 3-7 and 9-17 stand rejected under U.S.C. § 102(e) as being anticipated by U.S. Patent 6,420,526 ('526) or U.S. Patent 6,504,010 ('010) forth in the previous Office Action, mailed 2/27/04. The Applicants respectfully disagree.

Independent claims 1, 7, and 12, and their dependents concern methods of modulating an inflammatory and immune response, and decreasing myeloid cell activation by decreasing or altering the activity of the DAP12/TREM-1 complex.

1. The Applicants believe that the Examiner and the Applicants have inadvertently compared the incorrect SEQ.ID.NO: of the claimed invention with the polypeptide in the '526 and '010 patents. The Applicants mistakenly used SEQ.ID.NO:1, a nucleic acid sequence, where in fact SEQ.ID.NO:2, a polypeptide sequence should have been used. Notwithstanding, the Applicants assert that SEQ.ID.NO:2 of the claimed invention cannot be 100% identical to the SEQ.ID.NO:478 of the '526 patent nor SEQ.ID.NO:1825 of the '010 patent if the length of the former protein is 150 amino acids while the length of the latter proteins are 234 amino acids. The SEQ.ID.NO:2 is an entirely different chemical compound with unique features not previously recognized nor anticipated. For example, the transmembrane spanning portion of the full length TREM-1 protein in '526 and '010 is absent in the TREM-1 of SEQ.ID.NO:2 of the claimed invention. Therefore this soluble unanchored TREM-1 splice variant competitively inhibits the TREM-1 ligand. Thus, the functional distinction is certainly not inherent and certainly not anticipated. Inherent anticipation requires that the missing descriptive material is "necessarily present," not merely probable or possibly present, in the prior art. Inherency does not embrace probabilities or possibilities. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1951 (Fed. Cir. 1999).

Thus, the '526 and '010 patents could not have anticipated nor inherently described the claimed invention.

2. However, in order to advance prosecution of the patent application the Applicants have amended claims 1, 12, 13, and 14 without prejudice and without acquiescence to read on "decreasing". The '526 patent does not teach decreasing the immune response nor decreasing myeloid cell activation, but instead suggests differentiation and/or proliferation of neutrophils. Similarly, the '010 patent teaches immunogenic uses, that is, evoking an immune response. Cleary the Applicants' claimed invention does not teach to evoke immunogenic responses. As stated above, inherent anticipation requires that the missing descriptive material is "necessarily present," not merely probable or possibly present, in the prior art. Inherency does not embrace probabilities or possibilities. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1951 (Fed. Cir. 1999).

Thus, in view of the above arguments and amendments, the Applicants respectfully request removal of this rejection.

IV. Conclusion

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Applicants believe no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. 10023489 from which the undersigned is authorized to draw.

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Respectfully submitted,

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